DEVELOPMENT OF ANTI ALLERGY FROM NATURAL PRODUCT

Zullies Ikawati[(a)], Kartono Sudarman[(b)]
Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia

Allergy prevalence overall has been increasing since the early 1980s across all age, sex and racial groups. Allergy is the fifth leading chronic disease in the U.S. among all ages, and the third most common chronic disease among children under 18 years old. This disease is not life threatening, however, it highly influences patient quality of life. In Indonesia, the prevalence of allergic disease tend to increase by 30 percents per year.

Allergic reactions manifest clinically as anaphylaxis, allergic asthma, urticaria, angioedema, allergic rhinitis, some types of drug reactions, and atopic dermatitis. These reactions tend to be mediated by IgE, which differentiates them from anaphylactoid reactions that involve IgE-independent mast cell and basophil degranulation. Mast cells are necessary for the development of allergic reactions, through cross-linking of their surface receptors for IgE (Fc?RI) leading to degranulation and the release of vasoactive, proinflammatory, and nociceptive mediators that include histamine, IL-6, IL-8, PGD2, tryptase, and vascular endothelial growth factor (VEGF).

The management of allergy involves several steps, which include allergen avoidance, medication, and immunotherapy. The medication for allergic treatment may have several mechanisms, i.e. histamine receptor blockade, mast cells stabilization, and suppression of immune system. Other medications are also often used for alleviating the clinical symptoms.

The use of herbal medicines has increased in recent years. Many medicinal plants provide relief of symptoms comparable to those obtained from allopathic medicines. Specific chemical derivatives have been isolated from many plant products that act on the mechanisms and mediators causing asthma and allergies. There are various plants which can be used as antiallergy, including asthma, which mostly come from Traditional Chinese Medicine. such as ASHMI, Mai Men Dong Tang, Ding Chuan Tang, etc.

Recently we are developing a combination of leave extract of Legundi (Vitex trifolia L.) and temulawak (Curcuma xanthorrhiza R) for anti allergic rhinitis. Several studies have examined the effect of Vitex trifolia and Curcuma xanthorrhiza on allergic disease. In in vitro study, we have reported that legundi leaves extract could inhibit histamine release from RBL-2H3 cell cultures induced by DNP-BSA antigen. Isolated compounds from legundi, viteosin-A, vitexicarpin and vitetrifolin-E, have been reported to have tracheospasmolytic activity, whereas curcumin has significantly inhibited ovalbumin (OVA)-induced airway constriction and airway hyperactivity. Another study showed the effect of curcumin as an anti-inflammatory agent via inhibition of immunological point extracellular

[(b)] Dr.Sardjito General Hospital, Yogyakarta, Indonesia

signal-regulated kinase (ERK), which activated the enzyme protein kinase C (PKC) and inhibited Syk kinase activity. In the in vivo study, the extract combination of Vitex trifolia leaves and Curcuma xanthorrhiza rhizome was reported to inhibit cutaneus anaphylaxis reaction and showed anti allergic activities through a mechanism related to inhibition of mast cells degranulation and tracheospasmolytic activity.

In a preclinical toxicity study, the Curcuma xathorrhiza extract has been proven to be not toxic at a dose of 960 mg/200 g BW for 90 days. The extract combination of legundi leaves and temulawak rhizomes (1:1) is also not toxic, with apparent LD50 of 17.1 g / kg in acute toxicity study and sub acute toxicity study. Clinical trials of phase I and phase II of the combination have also been carried out and showed promising results.

The phase I clinical trial was carried out to determine the safety and tolerability of the extract combination of legundi (Vitex trifolia L) leaves and temulawak (Curcuma xanthorrhiza Roxb) rhizome in healthy volunteers.The trial employed randomized and double blind design with 30 healthy volunteers divided randomly into 3 groups. Each participant in groups 1, 2, and 3 received extract combination of legundi leaves and temulawak rhizomes with the dose of 1500, 4500, and 9000 mg/day, respectively. The extracts were administered orally three times daily for 14 consecutive days. The primary outcomes measured were the absence of tolerability and side effects. The secondary outcomes measured were changes in renal and liver functions, and physical examination before and after drug administration (pre and post control group design). The results showed that the extract combination at 1500 mg/day and 4500 mg/day were well tolerated and safe, as seen from the absence of the drug-induced changes in the renal and liver function. However, there were significant changes in the levels of AST and serum creatinine after administration of the extract combination with 9000 mg/day ($p < 0.05$). There were no significant side effects in the Group 1 and 2, while the thrush and decrease of blood pressure were reported after 9000 mg/day. Thus, extract combination of legundi leaves and temulawak rhizomes at 1500 mg/day and 4500 m /day were found to be well tolerated and safe in the subjects.

In the phase II clinical trial, the extract combination was examined for the anti allergic effect in rhinitis allergy patients. A randomized double-blind placebo-controlled study was conducted in 33 patients, which were divided into 3 groups receiving placebo, 1500mg/day, and 4500mg/day of extract combination, respectively. Each extract was administered 3 times daily for 14 days. The parameters of the clinical outcome were clinical symptoms (nasal congestion, nasal secretion, and sneezing), total IgE serum, and nasal swab eosinophil count, which were measured before and after treatment. The results showed that the extract combination at 4500mg/day has tended to decrease the levels of total IgE, which was significantly different compared to 1500mg/day (sig = 0,014) and placebo. However, with 1500mg/day and 4500mg/day, no significant difference was observed compared to placebo based on nasal swab eosinophil count (sig = 1,000). The doses of 1500 mg/day and 4500 mg/day have shown to improve clinical symptoms compared to placebo.

The phase III clinical trial is now in progress to confirm the efficacy of the extract combination for rhinitis allergy. Such a study is necessary for the development of herbal medicines to be accepted by clinician in formal medical care.

REFERENCES

PD PERSI, 2012, Setiap Tahun, Penderita Alergi di Indonesia Bertambah 30 Persen, http://www.pdpersi.co.id/content/news.php?catid=23&mid=5&nid=707, diakses pada bulan Juni 2012

Lawlor GJ, Fischer TJ, Adelman DC, eds. Manual of Allergy and Immunology. 3rd ed. Philadelphia, Pa: Lippincott-Raven; 1995

Kraft, S., S. Rana, M.H. jouvin, et al. 2004. The role of the Fc?RI beta-chain in allergic diseases. Int. Arch. Allergy Immunol. 135: 62-72.

Boesiger, J., M. Tsai, M. Maurer, et al. 1998. Mast cells can secrete vascular permeability factor/vascular endothelial cell growth factor and exhibit enhanced release after immunoglobulin E-dependent upregulation of Fce receptor I expression. J. Exp. Med. 188: 1135-1145

Xiu-Min Li, and Brown, L. 2009, Efficacy and mechanisms of action of traditional Chinese medicines for treating asthma and allergyJ Allergy Clin Immunol. 123(2): 297-308

Ikawati Z, Wahyuono S, and Maeyama K., 2001, Screening of Several Indonesian Medical Plants for their Inhibitory Effect on Histamine Release from RBL-2H3 Cells. J.Ethnopharmacol. 75, 249-256

Alam G, Wahyuono S, Ganjar IG, Hakim L, Timmerman H., 2002, Thracheospasmolitic activity viteosin A and vitexicarpine isolated from Vitex trifolia L., Planta med. 68, 1047-1049

Ram A, Das M, dan Ghosh B., 2003, Curcumin Attenuates Allergen-Induced Airway Hyperresponsiveness in Sensitized Guinea Pigs. Biol.Pharm.Bull. 26 (7), 1021-1024

Baek OS, Kang OH, Choi YA, Choi SC, Kim TH, Nah YH, Kwon DY, Kim YK, Kim YH, Bae KH, Lim JP, dan Lee YM., 2003, Curcumin Inhibits Protease-activated Receptor-2 and -4-mediated Mast cell Activation.Clin Chim, Acta. 338, 1-2

Ikawati Z, Yuniarti N, Prihartanto Y, 2008, Effect of extract combination of Vitex trifolia L leaves and Curcuma xanthorrhiza Roxb rhizome on active cutaneus anaphylaxis reaction induced by ovalbumin, Seminar Indonesia-Malaysia Update 2008. Mei 2008.

Melati R., Ikawati Z, Yuniarti N, 2008, Effect of extract combination of Vitex trifolia L leaves and Curcuma xanthorrhiza Roxb rhizome on histamine-induced tracheal contraction, Thesis, Faculty of Pharmacy, Gadjah Mada University (the article is originally published in Indonesian language)

Artanti AN., 2009, Sub acute toxicity study of purified extract of Curcuma xanthorrhiza, on liver function of Wistar rats, Thesis, Faculty of Pharmacy Gadjah Mada University (the article is originally published in Indonesian language)

Ikawati Z, Yuniarti N., 2010, Acute toxicity study of extract combination of Vitex trifolia leaves and Curcuma xanthorrhiza rhizome on wistar rats. International Congress of Phytopharm. St.Petersburg Rusia

Baroroh, HN., Ikawati, Z., Sudarman, K., 2011, A Safety Study of Extract Combination of Legundi (Vitex trifolia L.) Leaves and Temulawak (Curcuma xanthorrhiza R.) Rhizome as Anti-allergy in Healthy Volunteers, Int J Pharm Teaching & Practices, Vol.2, Issue 4, 165-170

Herdwiani, W., Ikawati, Z., Sudarman, K., 2012, Limited clinical trials of legundi leaves (Vitex trifolia l) and curcumae rhizomes (Curcuma xanthorrhiza roxb) extract on nasal swabs eosinophil in allergic rhinitis patients, submitted